Skin biopsy in netherton syndrome: a histological review of a large series and new findings

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Skin Biopsy in Netherton Syndrome: A Histological Review of a Large Series and New Findings

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Abstract: Netherton syndrome (NS) is a severe genetic skin disorder, with often delayed or misleading clinical signs. The histological features of skin biopsies, usually described as a psoriasiform hyperplasia, have only been reported in isolated case reports or small case series. The aim of this study is to define, for the first time, the precise histological pattern of cutaneous lesions, in a large cohort of skin biopsies from confirmed NS patients. The study included 80 consecutive skin biopsies from 67 patients taken between January 1995 and June 2014. All were from confirmed NS patients with either a negative lympho-epithelial Kazal-type–related inhibitor (LEKTI) immunohistochemistry and/or molecular confirmation by identified mutation in *SPINK5*. In this cohort, the most frequent histological finding was also psoriasiform hyperplasia, but there were additional, less common, or previously unreported findings, including compact parakeratosis with large nuclei, subcorneum or intracorneum splitting, presence of clear cells in the upper epidermis or stratum corneum, dyskeratosis, dermal infiltrate with neutrophils and/or eosinophils, and dilated blood vessels in the superficial dermis. An early confirmation of the diagnosis of NS is essential for improved patient management. Thus, in the situation of a patient with an unknown skin disorder and non specific clinical presentation, the dermatopathologist may now be able to suggest the diagnosis of NS based on these newly reported characteristics. However, LEKTI immunohistochemistry remains the essential diagnostic investigation in cases with misleading or nonspecific histological features and is mandatory for the definitive diagnosis of NS in all patients.

Key Words: Netherton syndrome, genodermatosis, histology, LEKTI antibody

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LEARNING OBJECTIVES

At the completion of this CME, the reader will be able to:

1. Provide a diagnosis of Netherton Syndrome in babies with erythroderma or an unknown skin disorder thought to be a disorder of cornification
2. Suggest the diagnosis of Netherton Syndrome based on newly reported characteristics
3. Describe the specific immunohistochemical staining seen in Netherton Syndrome and know to send a paraffin-fixed biopsy to a reference center.

INTRODUCTION

Netherton syndrome (NS, OMIM 256500) is a rare autosomal recessive genodermatosis. It is characterized by the triad of linear circumflex ichthyosis (Fig. 1A), trichorrhexis invaginata of hair and eyebrows, and atopic manifestations with high IgE levels in the serum. However, the onset of these typical clinical manifestations may be delayed and the clinical

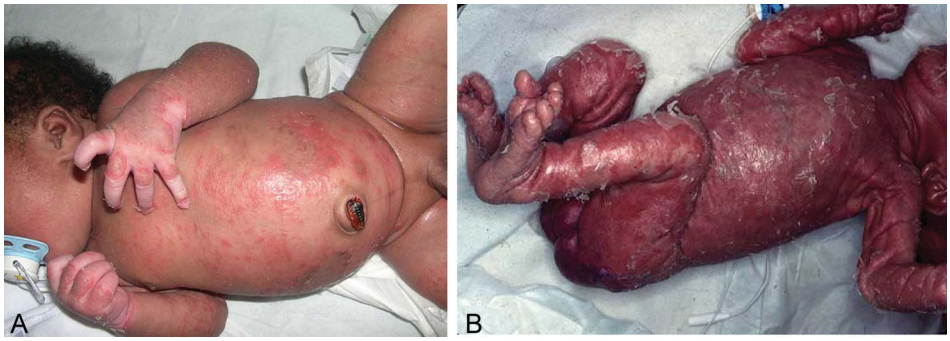

FIGURE 1. Collection by C. Bodemer: (A) infant with NS: typical aspect of linear circumflex ichthyosis; (B) infant with NS: congenital erythroderma.

features misleading. In infants, the disorder can present with severe and life-threatening erythroderma (Fig. 1B). In such cases, as well as in atypical adult cases, the diagnosis is challenging[1,2] and skin biopsy is mandatory.

The histological features seen in skin biopsies from NS patients, usually described as a psoriasiform hyperplasia, have only been reported in isolated case descriptions or small case series.[3–5] The aim of this study is to define the histological pattern of cutaneous lesions precisely and in a large cohort of skin biopsies from confirmed NS patients.

MATERIAL AND METHODS

This study included 80 consecutive skin biopsies from 67 NS patients analyzed retrospectively between January 1995 and June 2012 and prospectively from June 2012 until June 2014. All cases were collected from the informatics database of the Department of Pathology at Necker-Enfants Malades Hospital. Patients were either managed in our hospital or followed in other institutions with the skin samples provided to us for diagnostic confirmation.

Only skin biopsies with either negative lympho-epithelial Kazal-type–related inhibitor (LEKTI) immunohistochemistry (IHC) and/or a molecular confirmation of NS were included. LEKTI is a serine protease inhibitor encoded by serine protease inhibitor Kazal-type 5 (*SPINK5*), the causative gene of the NS.[6,7] For cases before 2000, LEKTI IHC was performed retrospectively. LEKTI was considered negative if the granular layer and/or inner root sheath of hair follicles were totally negative compared with a positive skin control (independently evaluated by 2 dermatopathologists, S.L.-M. and S.F.).

For histological analysis, skin biopsy specimens were fixed in 10% formalin, embedded in paraffin, divided into 3-μm-thick sections, and stained with hematoxylin, eosin, and saffron, and periodic acid–Schiff (PAS). IHC on skin biopsies, from 2000 to 2013, was performed using a monoclonal antibody against the D1–D6 domains of LEKTI (provided by Alain Hovnanian's laboratory) with a classical 3-step immunoperoxidase technique on formalin-fixed paraffin-embedded sections.[7] For biopsies from 2013 to 2014, we used a commercially available monoclonal antibody (clone SC48756). After deparaffinization, reactions were performed according to the automated system (A. Menarini Diagnosis system, Firenze, Italy) (Table 1). Staining was performed with the Bond polymer refine detection kit.

Each slide was examined retrospectively by 2 independent dermatopathologists (S.L.-M. and S.F.), and the following data were collected: pattern of the epidermal hyperplasia (psoriasiform, ichthyosiform, eczematiform, nonspecific), stratum corneum (present/absent, thickness, splitting, parakeratosis/orthokeratosis, microabcesses), stratum granulosum

TABLE 1. Methods for Immunohistochemistry With the Automatized System Bond, A. Menarini Diagnosis System

	Pretreatment	Duration, min	Dilution	Incubation, min
HPV antibody	ER1	30	1/2000	20
LEKTI antibody	ER2	20	1/250	20

TABLE 2. Histological Aspects of the 80 Examined Biopsies

Epidermal Changes	n (%)
Stratum corneum	
Absent	10 (12.5)
Split	46 (57.6)
Parakeratosic	65 (81.3)
Orthokeratosic	36 (45.0)
Microabcesses	21 (26.3)
Granular layer	
Normal or increased	38 (47.5)
Decreased	56 (70.0)
Absent	48 (60.0)
Clear cells	5 (6.3)
Spinous layer	
Spongiosis	7 (8.7)
Dyskeratosis	11 (13.8)
Intraepidermal exocytosis	5 (6.3)
Hyperplasia	
Psoriasiform	69 (86.3)
Not specific	20 (25.0)
Dermal Changes	**n (%)**
Inflammation	
Mild	59 (73.0)
Intense	17 (21.3)
Polynuclear neutrophils	19 (23.8)
Polynuclear eosinophils	26 (32.5)
Vessels	
Dilatation	41 (51.3)

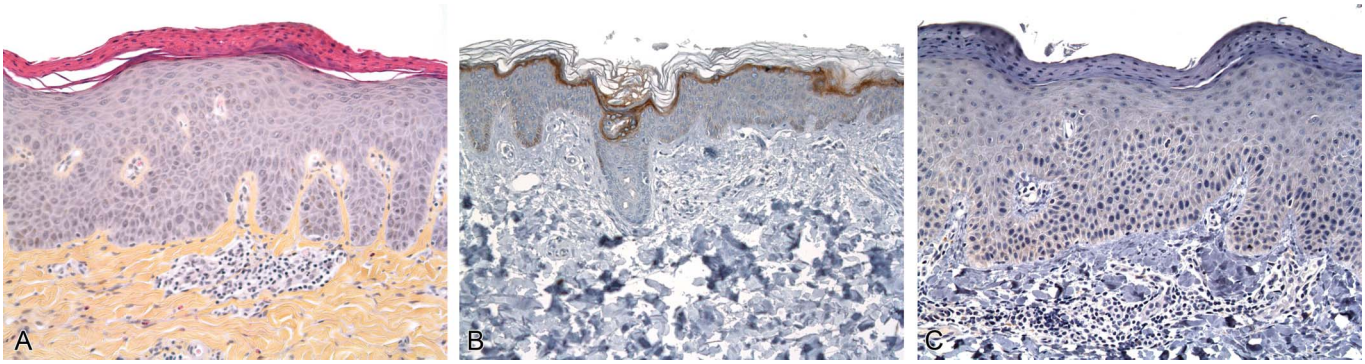

FIGURE 2. "Common" histological findings in Netherton syndrome. A, Hematein Eosin Saffron, ×200 magnification: compact parakeratosis (arrow), large nuclei, regular elongation of the rete ridges, absence of suprapapillary thinning; (B) LEKTI in normal skin, ×100; (C) LEKTI is negative in NS patient's skin, ×200 magnification.

(normal or increased/diminished/absent), Malpighian layer (spongiosis, dyskeratosis), inflammatory cell exocytosis, dermal inflammation (intensity, presence of neutrophils or eosinophils), dilatation of superficial blood vessels. An additional IHC study with anti–human papillomavirus (anti-HPV) antibody (Table 1) was performed in 5 cases with clear cells in the stratum corneum.

If there was discordance between the 2 examiners regarding the results of histology and/or IHC, the slides were reviewed simultaneously by both examiners using a 2-headed microscope and an agreement was reached.

RESULTS

Overall, 80 skin biopsies from 67 patients were included in the study. The patients' age ranged from 6 days to 80 years, with 50% of the patients being younger than 2 years. LEKTI IHC was negative in 100% of the skin biopsies. Molecular diagnosis was confirmed by *SPINK5* sequencing in all patients who were genetically tested (51 of 67 patients).

The overall histological findings are summarized in Table 2. Sums may be greater than 100% because several patterns regularly coexisted in single biopsies, demonstrating heterogeneity of the lesions within a single patient. The most frequently observed aspect was a psoriasiform hyperplasia with a hyperplastic epidermis and elongated regular rete ridges. This is different from that seen in psoriasis because of the absence of suprapapillary thinning and to the presence of a compact parakeratosis with large nuclei. A mild, dermal inflammatory infiltrate was often present (Fig. 2).

In addition to the psoriasiform hyperplasia, other changes were also observed. The stratum corneum was sometimes absent or split (Figs. 3A–C). Microabcesses were frequently observed (Fig. 4), with negative PAS staining in all but 1 case. Clear cells with a pseudoviral aspect (pseudokoilocytes, HPV staining negative) could be observed in the stratum granulosum or stratum corneum (Figs. 5A–C). The granular layer could be normal, absent, or diminished in the same biopsy. We also observed the coexistence of parakeratosis overlying an absent granular layer alternating with orthokeratosis overlying a normal granular layer (Fig. 6).

In 2 cases, the features were similar to those seen in autosomal recessive congenital ichthyosis, specifically compact hyperorthokeratosis with a thick granular layer and hyperplasic epidermis (Fig. 7).

Spongiosis was unusual (Fig. 8) while dyskeratosis was found in some cases.

Dermal inflammation was often mild but sometimes conspicuous (Fig. 9). When inflammatory cells were present, prominence of eosinophils was observed in almost a third of the cases, with or without epidermal exocytosis (Fig. 10A). In addition, dermal neutrophils were often observed, sometimes in a large number, with epidermal exocytosis and microabcesses (Fig. 10B). In some patients, histology revealed only

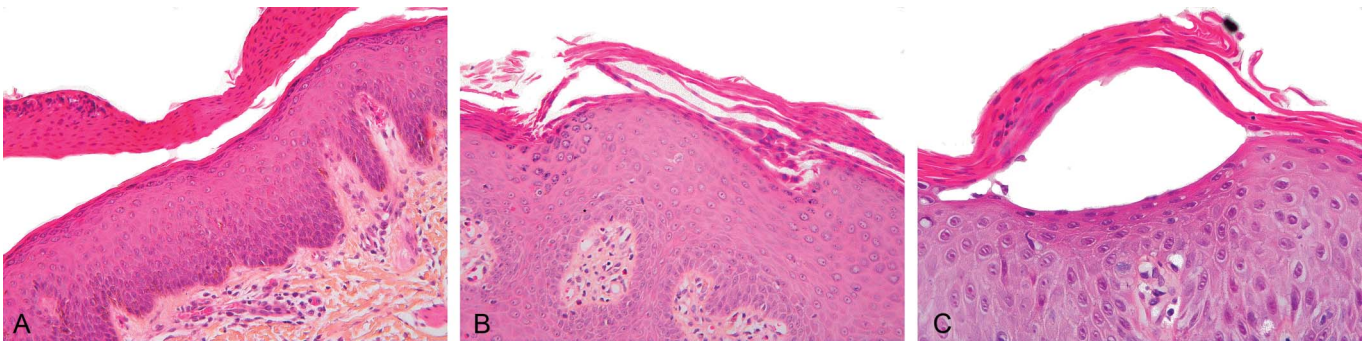

FIGURE 3. A, Hematein Eosin Saffron, ×200 magnification: complete splitting of the stratum corneum; (B) Hematein Eosin Saffron, ×200 magnification: splitting in multiple layers; (C) Hematein Eosin Saffron, ×400 magnification: pseudo-vesiculosus splitting.

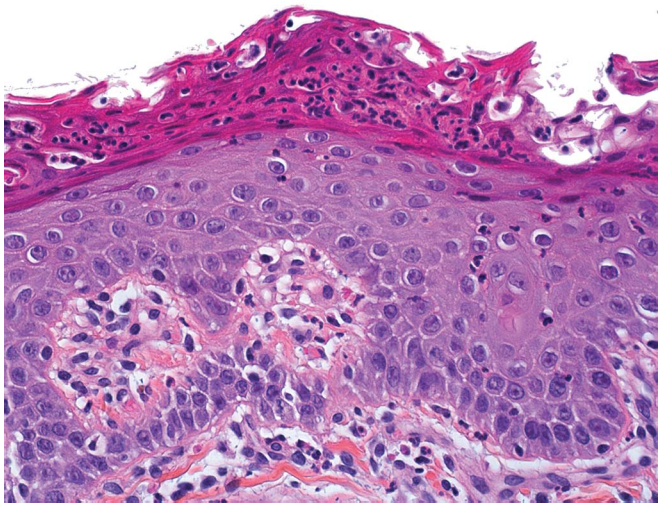

FIGURE 4. Hematein Eosin Saffron, ×400 magnification: multilocular microabcesses in the stratum corneum.

mild abnormalities such as a subtle splitting of a basket-weave stratum corneum (Fig. 11).

DISCUSSION

To our knowledge, this series, with 80 skin biopsies from 67 patients, is the largest study to report the histological patterns of NS. We confirm the high frequency of psoriasiform hyperplasia and describe previously unreported characteristics.

The clinical diagnosis of NS is difficult to make and often delayed, because the clinical triad of linear circumflex ichthyosis, trichorrhexis invaginata of hair and eyebrows, and atopic manifestations, which characterized NS in its first descriptions, are not always present. In addition, the typical hair shaft anomaly is exceptionally seen before the first year. The disease can be severe, and potentially life-threatening, with the occurrence of hypernatremic dehydration, seizures, diarrhea, and recurrent sepsis.[2] An early skin biopsy is very helpful in making the diagnosis, and we have reported 100% sensitivity and specificity in distinguishing NS from other conditions, mostly immunodeficiency syndromes, in neonatal and infantile erythroderma since LEKTI antibodies became available in 2000.[8]

For adults, linear circumflex ichthyosis may be easily recognized and hair shaft or eyebrow examination (dermoscopy[9] or light microscopy[10]) is useful as trichorrhexis invaginata is specific to NS. However, NS can also have unusual clinical features, such as atypical, chronic atopic dermatitis, or a nonspecific ichthyotic pattern. In all these cases, a skin biopsy is essential to make the correct diagnosis.

The largest series that includes morphologic descriptions of NS was published by Hausser and Anton-Lanprecht[3] and described 19 cases with seborrheic or psoriasiform dermatitis, parakeratosis, and the lack of a granular layer. This psoriasiform hyperplasia was also seen in most of our cases (86.3%). In addition, splitting of the subcorneum was often present in our skin samples, and, in some cases, the stratum corneum was totally absent.

Splitting of the subcorneum is biologically consistent, as *SPINK5* knockout mice display superficial peeling caused by stratum corneum detachment from the granular layer, and links this morphologic aspect to the causative genetic defect.[11] Furthermore, a recent review reported the overlap between 3 skin conditions in which cell–cell adhesion is impaired and stratum corneum detachment occurs, namely severe dermatitis–multiple allergies–metabolic wasting syndrome, type B peeling skin disease, and NS.[12] Such detachment of the stratum corneum was first reported by Comel,[13] and although splitting has been well described in studies using electron microscopy,[2,3,11] it is rarely reported using light microscopy.

Thus, despite being nonspecific, subcorneum splitting may be a helpful sign to look for by light microscopy.

A psoriasiform hyperplasia was often observed in our cases, but no suprapapillary thinning, as is seen in psoriasis, was noted. In our experience, spongiosis was uncommon, occurring in less than 10% of cases. This is in contrast to other authors who reported that spongiosis could be pronounced in the lower epidermal cell layers.[2]

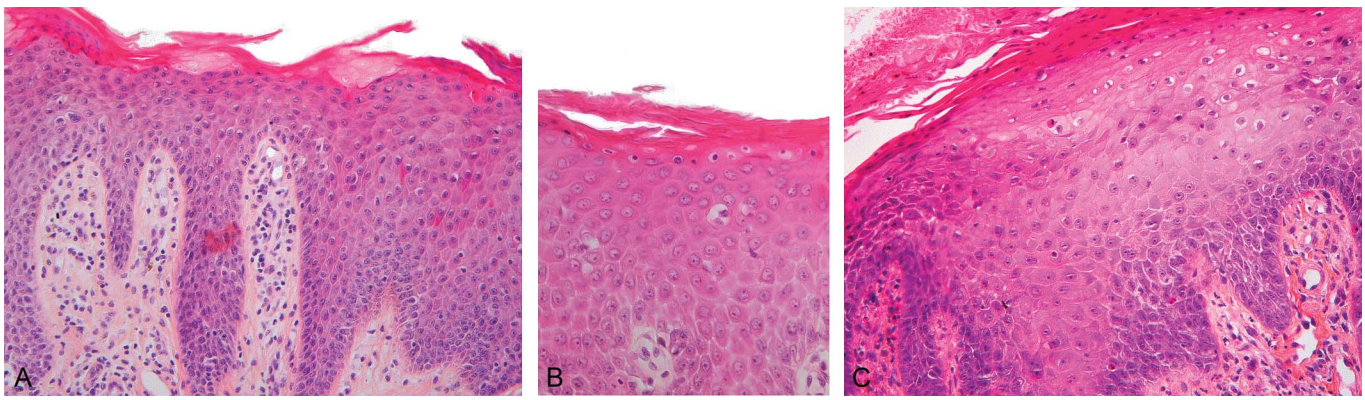

FIGURE 5. A, Hematein Eosin Saffron, ×400 magnification: clear cells in the stratum corneum (arrow); (B) Hematein Eosin Saffron, ×200 magnification: clear pseudo-koilocytic cells in the stratum granulosum (arrow); (C) Hematein Eosin Saffron, ×200 magnification: clear cells in the upper spinous layer (arrow). See also spongiosis, rarely observed in our series. HPV immunochemistry was negative in these 5 cases.

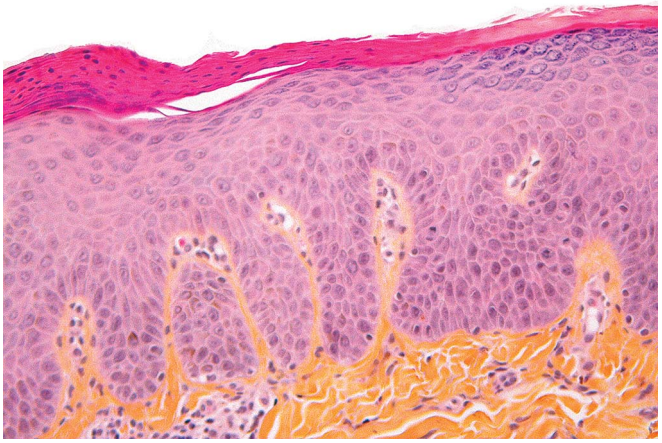

FIGURE 6. Hematein Eosin Saffron, ×200 magnification: coexistence of parakeratosis (arrow) overlying an absent granular layer alternating with orthokeratosis (double arrow) and normal granular layer.

In our series, we found that parakeratosis in NS is compact and shows large nuclei that is very different from psoriatic parakeratosis. Ong and Harper[2] described that the outermost nucleated cell layer does not appear to flatten normally. Similar findings, that is, a psoriasiform pattern with mild, perivascular inflammatory infiltrate in the superficial dermis, were described by Weedon[4] and Metze.[5] Biopsies from the center of the lesions were reported to show aspects of atopic dermatitis rather than psoriasiform features.[5] We were unable to confirm this observation as our skin biopsies were either taken at scaly margins or from areas without specific information. No correlation could be established between the type of inflammatory cells (neutrophils or eosinophils) and the aspect of the epidermis (psoriasiform or spongiotic).

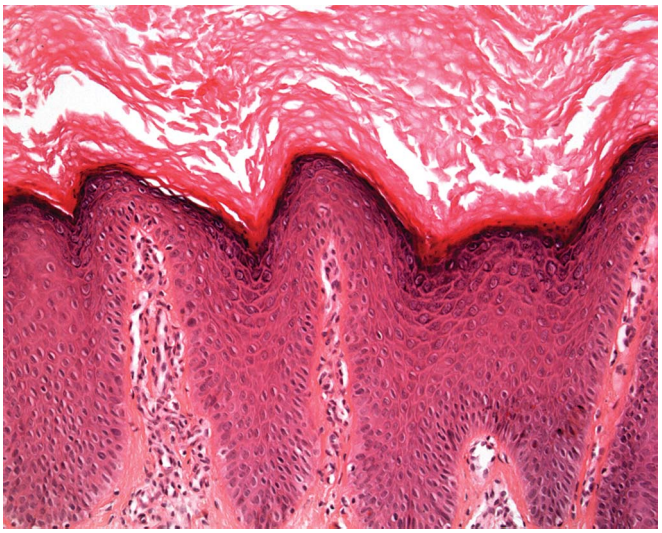

FIGURE 7. Hematein Eosin Saffron, ×200 magnification: NS with an aspect of autosomal recessive congenital ichthyosis (compact hyperorthokeratosis, thick granular layer, and hyperplastic epidermis).

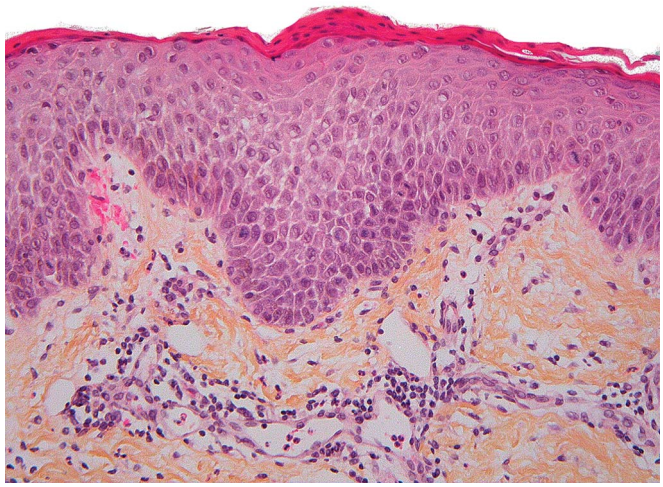

FIGURE 8. Hematein Eosin Saffron, ×200 magnification: spongiosis.

In our series, the inflammation was usually moderate and both neutrophils and eosinophils were commonly observed. PAS was always negative. In common inflammatory skin diseases, the inflammatory infiltrates are more frequently composed of histiocytes and lymphocytes. The presence of a predominent eosinophilic infiltrate in one of our 3 cases, rarely reported before, may be explained by the secretion of specific chemotactic mediators in direct relation with the atopic diathesis of NS. In the series of Hausser and Anton-Lanprecht,[3] a variable dermal inflammatory infiltrate was described, with various cells including neutrophils associated with subsequent formation of small, intraepidermal, mostly superficial pustules or microabcesses.

In addition to the above, we observed several new histological anomalies. First was the presence of dyskeratotic cells, with no more than 1 to 3 cells that were always located in the upper spinous layer. This is not easily explained by the pathophysiology of NS and could be related to the use of topical products.

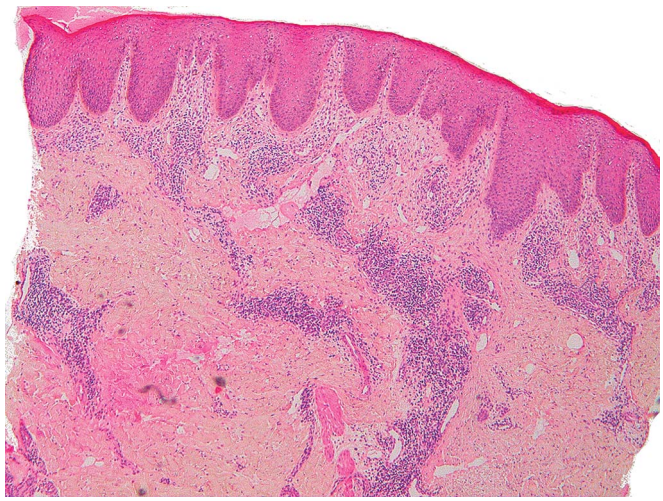

FIGURE 9. Hematein Eosin Saffron, ×50 magnification: marked superficial and middermal perivascular infiltrate.

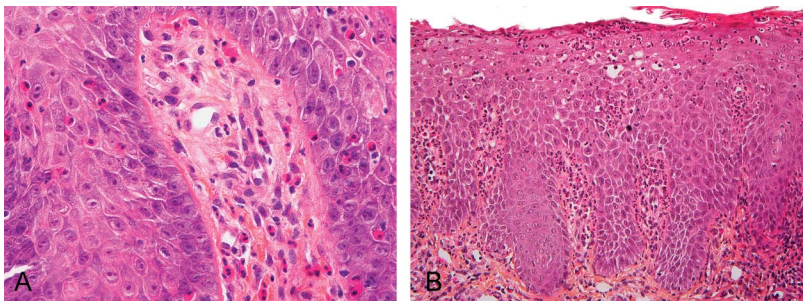

FIGURE 10. A, Hematein Eosin Saffron, ×400 magnification: numerous dermal and intraepidermal eosinophils. B, Hematein Eosin Saffron, ×200 magnification: numerous dermal and intraepidermal neutrophils and eosinophils, intraepidermal exocytosis.

Second, we noted the presence of dilated blood vessels in the upper dermis in more than 50% of our cases. This may correlate with the degree of erythema and/or erythroderma. However, the histological aspects can be misleading, may mimick other conditions such as autosomal recessive congenital ichthyosis, or be entirely nonspecific.

The use of IHC with LEKTI-specific antibodies to demonstrate the absence of the protein in the epidermis (Fig. 3C) allows for the definitive diagnosis of NS.[7,8,14,15] In normal skin, LEKTI IHC is always positive in the granular layer and the inner root sheath of hair follicles (Fig. 3B). One hundred percent of the cases in our series were LEKTI negative. A definitive diagnosis of NS requires LEKTI negativity within the inner root sheath of the follicular ostia, because the granular layer may be missing in both NS and other conditions.

NS is a severe genetic skin disorder with a heterogeneous clinical presentation that can be misleading and delay accurate diagnosis. Early confirmation of the diagnosis is essential for proper patient management. Thus, a skin biopsy is mandatory if typical hair shaft anomalies are not found. In this study, we show that the histological features of NS are not restricted to the classically described "psoriasiform aspect," and additional histological characteristics can be helpful in correctly making the diagnosis. Compact parakeratosis with large nuclei, subcorneum or intracorneum splitting, absence of stratum corneum, frequent microabcesses (PAS negative), elongated rete ridges without suprapapillary thinning, dermal infiltrates rich in neutrophils and/or eosinophils, and dilated blood vessels in the superficial dermis are all seen in NS and, especially when seen in combination, can aid correct diagnosis. For patients with an unknown skin disorder and a nonspecific clinical presentation, the dermatopathologist may now be able to propose a diagnosis of NS based on light microscopy. However, performing LEKTI staining remains mandatory for the definitive diagnosis of NS in all patients.

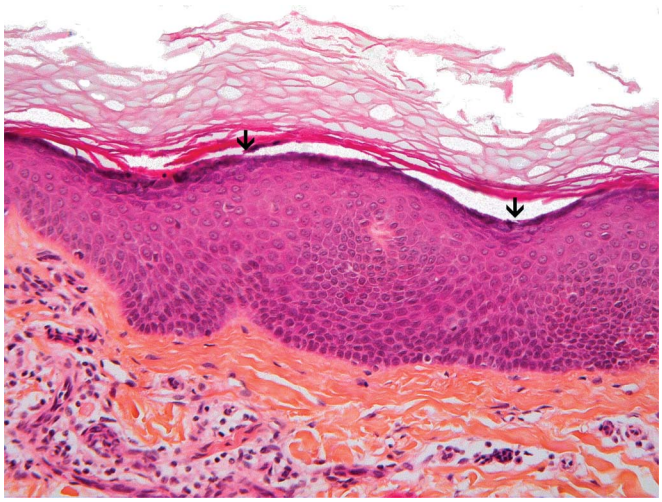

FIGURE 11. Hematein Eosin Saffron, ×200 magnification: subnormal skin biopsy, with a subtle splitting (arrows) of a basket-weave stratum corneum.

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CME EXAM
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CME EXAMINATION
February 2016

Please mark your answers on the ANSWER SHEET.

At the completion of this CME, the reader will be able to provide a diagnosis of Netherton Syndrome in babies with erythroderma or an unknown skin disorder thought to be a disorder of cornification, suggest the diagnosis of Netherton Syndrome based on newly reported characteristics and describe the specific immunohistochemical staining seen in Netherton Syndrome and know to send a paraffin-fixed biopsy to a reference center.

1. The gene implicated in Netherton syndrome (NS) is:

   A. LEKTI
   B. TGM5
   C. SPINK5
   D. ABCA12

2. NS is characterized by a clinical triad of:

   A. Erythroderma, photophobia, trichorrhexis nodosa
   B. Linear circumflex ichthyosis, trichorrhexis invaginata, atopic manifestations
   C. Psoriasis, pili torti, diarrhea
   D. Linear circumflex ichthyosis, xerostomia, pili canaliculi

3. Which of the following is not true concerning NS?

   A. Histology often demonstrates eczematiform lesions
   B. Sub-corneal splitting is frequently observed
   C. Mast cells are numerous in the dermal infiltrate
   D. The parakeratosis is compact

4. Potentially misleading histological findings in NS that can mimic other genodermatoses include:

   A. Autosomal recessive ichthyosis
   B. Epidermolytic ichthyosis
   C. Erythrokeratoderma Variabilis
   D. Hailey–Hailey disease

5. A histological diagnosis of NS requires:

   A. A formalin-fixed biopsy for standard histology and a frozen biopsy for immunohistochemistry with LEKTI antibody
   B. A formalin-fixed biopsy for standard histology and a blood sample for indirect immunofluorescence with LEKTI antibody
   C. A formalin-fixed biopsy for standard histology and immunohistochemistry with LEKTI antibody
   D. A frozen biopsy for immunohistochemistry with LEKTI antibody only, standard histology is not helpful.

ANSWER SHEET FOR THE AMERICAN JOURNAL OF DERMATOPATHOLOGY
CME PROGRAM EXAM
February 2016

Please answer the questions on page 89 by filling in the appropriate circles on the answer sheet below. Please mark the one best answer and fill in the circle until the letter is no longer visible. To process your exam, you must also provide the following information:

Name (please print): _____
Street Address _____
City/State/Zip _____
Daytime Phone _____
Specialty _____

1. Ⓐ Ⓑ Ⓒ Ⓓ Ⓔ
2. Ⓐ Ⓑ Ⓒ Ⓓ Ⓔ
3. Ⓐ Ⓑ Ⓒ Ⓓ Ⓔ
4. Ⓐ Ⓑ Ⓒ Ⓓ Ⓔ
5. Ⓐ Ⓑ Ⓒ Ⓓ Ⓔ

Your evaluation of this CME activity will help guide future planning. Please respond to the following questions below.

Please rate these activities (1 — minimally, 5 — completely)	1 2 3 4 5
These activities were effective in meeting the educational objectives	O O O O O
These activities were appropriately evidence-based	O O O O O
These activities were relevant to my practice	O O O O O

Please rate your ability to achieve the following objectives, both before and after this activity: 1 (minimally) to 5 (completely)	Pre 1 2 3 4 5	Post 1 2 3 4 5
1. Provide a diagnosis of Netherton Syndrome in babies with erythroderma or an unknown skin disorder thought to be a disorder of cornification	O O O O O	O O O O O
2. Suggest the diagnosis of Netherton Syndrome based on newly reported characteristics	O O O O O	O O O O O
3. Describe the specific immunohistochemical staining seen in Netherton Syndrome and know to send a paraffin-fixed biopsy to a reference center	O O O O O	O O O O O

How many of your patients are likely to be impacted by what you learned from this activity?
O <20% O 20-40% O 40-60% O 60-80% O >80%

Do you expect that these activities will help you improve your skill or judgment within the next 6 months? (1 — definitely will not change, 5 — definitely will change)	1 2 3 4 5
	O O O O O

How will you apply what you learned from these activities (mark all that apply):

In diagnosing patients O	In making treatment decisions O
In monitoring patients O	As a foundation to learn more O
In educating students and colleagues O	In educating patients and their caregivers O
As part of a quality or performance improvement project O	To confirm current practice O
For maintenance of board certification O	For maintenance of licensure O

Please list at least one strategy you learned from this activity that you will apply in practice:

How committed are you to applying these activities to your practice in the ways you indicated above? (1 — minimally, 5 — completely)	1 2 3 4 5
	O O O O O

Did you perceive any bias for or against any commercial products or devices?	Yes	No
If yes, please explain:	O	O

How long did it take you to complete these activities? _____ hours _____ minutes
What are your biggest clinical challenges related to dermatopathology?

[ ] Yes! I am interested in receiving future CME programs from Lippincott CME Institute! (Please place a check mark in the box)

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